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Cancer Prevention Research

Review

Obesity, Energy Balance, and Cancer: New Opportunities for Prevention

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Abstract

Obesity is associated with increased risk and poor prognosis for many types of cancer. The mechanisms underlying the obesity-cancer link are becoming increasingly clear and provide multiple opportunities for primary to tertiary prevention. Several obesity-related host factors can influence tumor initiation, progression and/or response to therapy, and these have been implicated as key contributors to the complex effects of obesity on cancer incidence and outcomes. These host factors include insulin, insulin-like growth factor-I, leptin, adiponectin, steroid hormones, cytokines, and inflammation-related molecules. Each of these host factors is considered in the context of energy balance and as potential targets for cancer prevention. The possibility of prevention at the systems level, including energy restriction, dietary composition, and exercise is considered as is the importance of the newly emerging field of stem cell research as a model for studying energy balance and cancer prevention. *Cancer Prev Res; 5(11); 1260–72. ©2012 AACR.*

Introduction

The prevalence of obesity has doubled globally, reaching pandemic proportions over the past 30 years. Today, 65% of the world's population lives in countries where obesity kills far more people than underweight (1). Obesity increases the risk for colon, endometrial, esophageal, renal, pancreatic, and postmenopausal breast cancer, and the list continues to grow (2). More recent epidemiologic studies confirm the associations indicated above and provide probable evidence for associations of obesity with gallbladder and hepatocellular carcinomas (3, 4), as well as suggestive evidence for associations with ovarian and thyroid cancers. Obesity is also associated with increased risk for several hematologic malignancies including plasma cell myeloma, Hodgkin and non-Hodgkin lymphoma, and leukemia (5, 6). Moreover, obesity at the time of diagnosis is acknowledged to be a poor prognostic factor for several tumor types (7). Although difficult to investigate or implement in humans, caloric restriction studies in multiple organisms have provided significant insights into the mechanistic links between energy balance and cancer and suggest novel approaches for interventional targets (8).

Many energy balance–related physiologic processes, including appetite, energy expenditure, body temperature control, and nutrient and energy metabolism are regulated by hormones, cytokines, and other host factors. There is increasing evidence that alterations in, and cross-talk between cytokines and growth and inflammatory factors, for example, insulin, insulin-like growth factor (IGF)-I, leptin, and adiponectin, mediate many of the antiproliferative, proapoptotic, and anticancer effects of caloric restriction or negative energy balance (8, 9). Given the universal need for energy, multiple pathways with ample cross-talk and redundancies have evolved to assure cell survival, regardless of whether cells are healthy, transformed, or cancerous. These pathways may be even more highly evolved in the preneoplastic or neoplastic cell to support increased energy needs for enhanced proliferation and uncontrolled cell growth (10).

Selected proposed mechanisms that undergird energy balance effects on cancer were addressed by experts in a recent workshop, entitled "The Role of Obesity in Cancer Survival and Recurrence," convened by the Institute of Medicine's (IOM) National Cancer Policy Forum in Washington, DC (October 31–November 1, 2011). This article provides a summary of the mechanisms that were addressed and reframes this information to address their potential to serve as targets for cancer prevention; a detailed summary of this original workshop and accompanying slides are available online (11).

While controversy remains, the preponderance of clinical evidence supports a role for obesity's influence on the incidence and course of many cancers (2–6) with strong support for potential mediators derived from preclinical

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mechanism-based studies, which are further supported by clinicoepidemiologic observations. These preclinical, mechanistic studies are the major focus of this report with related clinicoepidemiologic research noted to provide translational relevance.

Overview

Figures 1 and 2 provide a systems overview of the multitude of extracellular and downstream intracellular pathways by which energy balance modulates cell growth, carcinogenesis, and tumor promotion (12). Note that these multiple factors interact at numerous levels and share extensive cross-talk. Thus, attempts to block a pathway with a specific inhibitor may be undermined by collateral effects on alternate pathways. Therefore, targeting multiple pathways is likely to be necessary to develop prevention and control regimens that can effectively exploit the obesity–cancer linkage.

Hormones, Growth Factors, and Intracellular Downstream Targets

Insulin

Clinical and epidemiologic evidence suggests that elevated levels of circulating insulin or C-peptide (cleavage product of proinsulin), are associated with increased risk and/or poor prognosis of endometrial, pancreatic, renal, prostatic, colon, and pre- and postmenopausal breast cancers (9, 12, 13). Insulin exerts tumor-enhancing effects directly via the insulin receptor (IR) or hybrid IR/IGF-IR's on preneoplastic and neoplastic cells. High circulating levels of insulin also upregulate hepatic synthesis of IGF-I and downregulate IGF binding protein (BP) production (13). The binding of insulin or IGF-I to cell surface receptors activates the phosphatidylinositol-3 kinase (PI3K)/Akt pathway (leading to downstream activation of the mTOR complex), and/or the mitogen-activated protein kinase (MAPK) pathway; both pathways are central regulators of cell growth and mitogenesis (9, 12).

In a mouse model of hyperinsulinemia, mammary tumor growth and metastasis is enhanced by endogenous hyperinsulinemia activating the IR/IGF-IRs on tumor cells. Reducing hyperinsulinemia and blocking IR/IGF-IR activation with a specific tyrosine kinase inhibitor (TKI) decreases tumor burden (14, 15). These data strongly suggest that endogenous hyperinsulinemia may be one obesity-related factor enhancing cancer growth and metastases. Moreover, in women with breast cancers, a worse prognosis was noted in those with higher circulating insulin level as well as those with increased IR expression in tumor tissue (16).

The effect of insulin on cancer cells has furthermore been shown to activate an IR subtype (IR-A) that is expressed by fetal tissues and cancer cells. IR-A mediates insulin's metabolic functions and is more mitogenic than the other splice variant, IR-B, expressed in muscle, fat, and liver (17).

The presence of IR-A on tumor cells may provide a specific target to block insulin stimulation of cancer cell growth without interfering with its normal role in energy metabolism. Targeting the intracellular PI3K–Akt pathway, downstream of the IR, may also provide an alternative approach to specifically interrupt the growth promoting activities

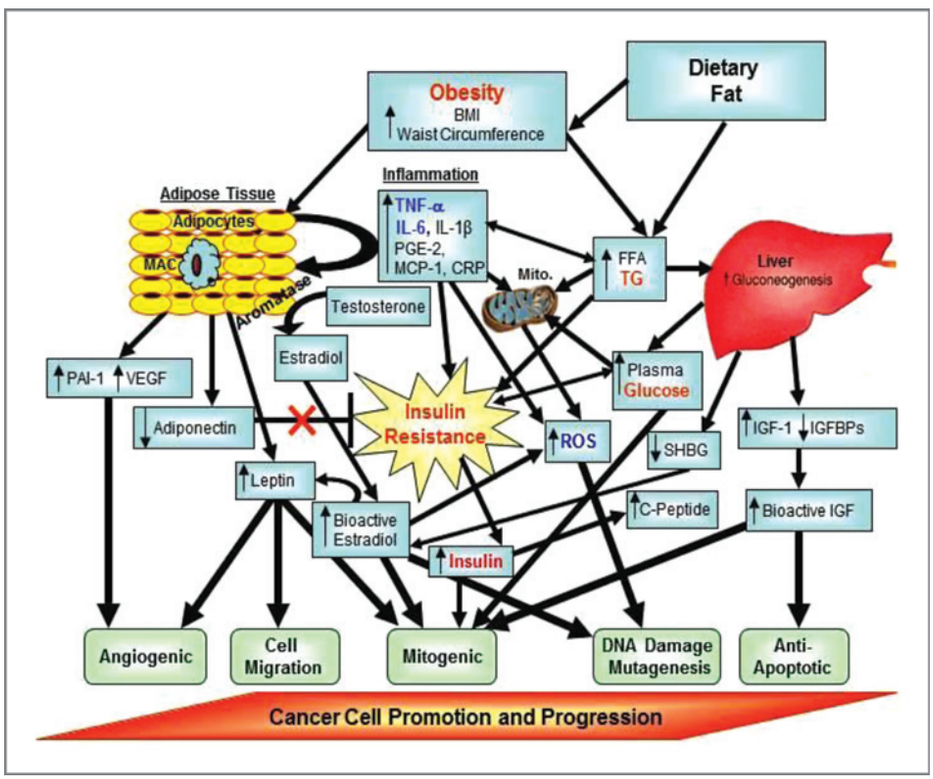

Figure 1. Peptide growth factors, adipokines, nutrients, and other putative factors involved in regulating obesity-related carcinogenesis. Adapted with permission from Nock and Berger (12) and Cowey and Hardy (160). Factors denoted in bold red text are core features of the metabolic syndrome. Factors denoted in bold blue text are additional features that may also be components of the metabolic syndrome. Abbreviations used: FFA, free fatty acids; IGFBP, insulin-like growth factor binding protein; IL-1β, interleukin-1β; MAC, macrophage; Mito, mitochondria; PAI-1, plasminogen activator inhibitor-1; ROS, reactive oxygen species; SHBG, steroid hormone-binding globulin; TG, triglycerides.

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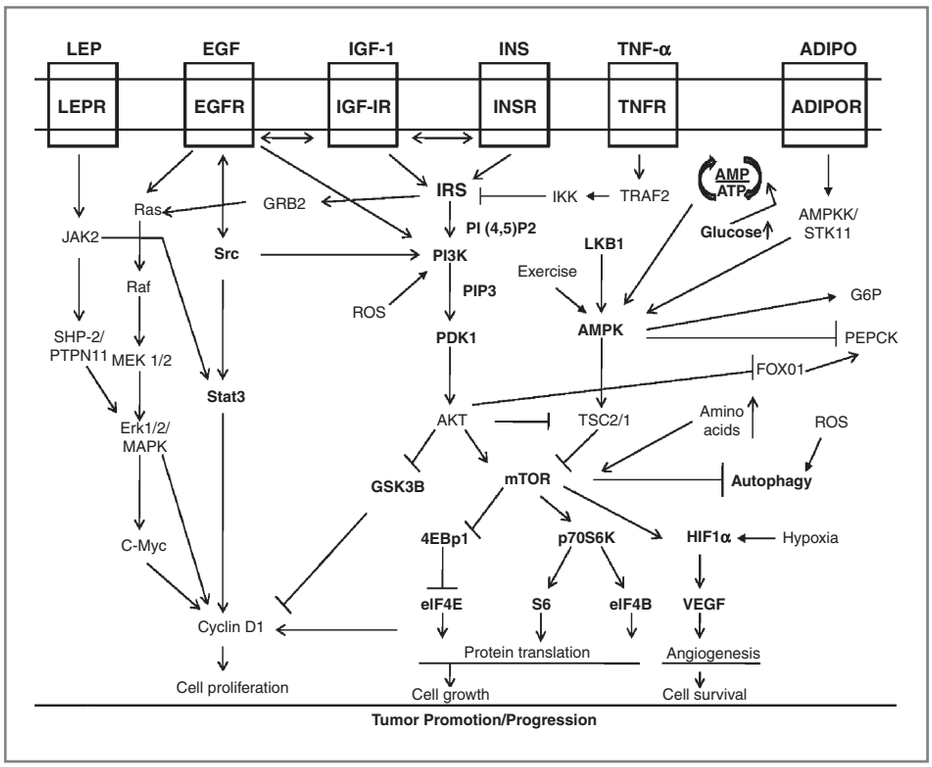

Figure 2. Intracellular pathways of growth factors involved in obesity-associated cancer promotion and progression. Adapted with permission from Nock and Berger (12) and Moore and colleagues (118).

of insulin associated with hyperinsulinemia and insulin resistance.

Insulin-like growth factor-I

IGF-I is a major endocrine and paracrine regulator of tissue growth and metabolism as it both suppresses apoptosis and initiates cell-cycle progression from G_1 to S-phase by activating PI3K/Akt and MAPK signal transduction pathways and modulating cyclin-dependent kinases (13). Epidemiologic evidence also supports the hypothesis that increased circulating IGF-I is associated with increased risk and/or worse prognosis for several types of human cancers (8, 18). IGF-I may act either directly on cells via IGF-IRs or IRs (or even IGF/IR hybrid receptors), or indirectly through interaction with other cancer-related molecules, for example, the tumor suppressor, p53 (13). In numerous animal models, obesity increases, while caloric restriction decreases circulating IGF-I and tumor development and progression (8, 9, 19), whereas exogenous IGF-I infusion rescues tumor growth in caloric restricted mice (8, 18). Similar to caloric restriction, genetic reduction of circulating IGF-I in liver-specific IGF-I–deficient mice decreases tumor progression in models of colon, skin, mammary, and pancreatic cancer (20, 21). Interestingly, IGF-I–deficient mice, which are resistant to growth of several tumor types, have markedly elevated insulin and adipokine levels, but a 65% reduction in IGF-I (22), suggesting that IGF-I may be a central determinant of energy balance modulation of cancer in experimental models (8). However, the obesity-IGF-I relationship is more complex in humans, as total circulating IGF-I levels are often not elevated in obese individuals (23, 24). The hyperinsulinemia associated with obesity can decrease production of IGF BPs (particularly BP1 and 2), and thus increase the levels of biovailable IGF-I to enhance signaling through the IGF-IR (13). Agents that block the IGF-IR to decrease IGF-I signaling, and to some extent insulin signaling are under clinical development and may serve as cancer prevention and control agents; however, selectivity for tumor cells and unwanted metabolic effects remain a challenge for these agents (25).

VEGF

VEGF is induced by insulin and IGF-I (26), and mediates cancer cell proliferation and tumor growth by inducing angiogenesis. Produced by both adipocytes and tumor cells, higher circulating levels of VEGF are seen in obese animals (27) and humans (28), and decrease upon weight loss (29). A recent and growing body of evidence in humans suggests strong associations between VEGF levels and aggressive cancers (30, 31). Several TKIs that interfere with VEGF activity have been developed and could play a role in cancer prevention.

Steroid Hormones

Estrogen

Estrogen is produced in large amounts by the ovary via conversion of androgens (testosterone and androstenedione) in a reaction mediated by aromatase. After menopause, when the ovary ceases to function, estrogens continue to be produced by other tissues, with a major

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contributor being adipose tissue. Multiple lines of evidence suggest a key role for estrogen in explaining the increased risk of hormone receptor–positive breast cancer in obese postmenopausal women. Estrogen has also been implicated in the pathogenesis of a subset of endometrial cancers arising in obese women (32). Total and free estrogen levels are increased in the plasma of obese as compared with normal weight postmenopausal women (33). Estrogen binds to estrogen receptor-α and thereby stimulates cell proliferation and inhibits apoptosis (34). Estrogens can also induce VEGF and angiogenesis (35). In addition to driving tumor formation via estrogen receptor-α–dependent effects, estrogen can be metabolized into DNA-reactive metabolites that potentially induce mutagenesis (34). There is clear evidence of the growth promoting effects of estrogens from studies in animals (36). The importance of targeting estrogen as a preventive intervention is underscored by clinical data. Tamoxifen and raloxifene, functioning as selective estrogen receptor modulators, have been shown to significantly reduce the development of postmenopausal breast cancer (37), and these agents are effective secondary preventive agents in women who have undergone primary treatment of breast cancer (38). Raloxifene has also been shown to have a preventive effect on the development of uterine cancer (39). Recently, treatment with exemestane, an aromatase inhibitor, was found to decrease the relative risk of invasive breast cancer by 65% (40). Notably, many of the women enrolled in this trial were overweight or obese.

A major unanswered question concerns the relative importance of peripheral versus breast adipose tissue as the primary source of the estrogen that drives tumor formation and progression in obese postmenopausal women. Until recently, it was assumed that the mildly elevated levels of estrogen in venous blood of obese versus lean postmenopausal women could account, in part, for the observed increased risk of breast cancer. However, 2 recent findings have challenged this explanation. First results from the Women's Health Initiative Estrogen-Alone Trial indicate that administration of estrogen only hormone replacement therapy was associated with a lower incidence of invasive breast cancer in postmenopausal women among those who have had previous hysterectomy (41). Second, as detailed later, obesity was recently found to cause breast inflammation, elevated aromatase levels, and activation of estrogen receptor-α–dependent gene expression (42–44). Collectively, these recent findings highlight the complexity of estrogen biology but offer clues to the development of future preventive strategies.

Testosterone and other androgens

The role of androgens in prostate cancer is significant as estimates indicate that 80% to 90% of prostate cancer is dependent on circulating androgens for growth (45) and androgen deprivation directly or through administration of LHRH antagonists, is a highly successful mainstay of antiprostate cancer therapy (46). However, it is difficult to describe how obesity, androgen exposure, and prostate cancer risk are interrelated as obesity is associated with lower circulating levels of androgens in men (47), and there is no strong association between obesity and prostate cancer risk overall (48). However, there is a significant association between obesity and aggressive prostate cancer (49), which may relate to the cross-talk between androgens and circulating cytokines [e.g., interleukin-6 (IL-6)] and growth factors (e.g., IGF-I and EGF), which can activate the androgen receptor and stimulate JAK/STAT and the PI3K/Akt/mTOR pathways, respectively (50), or the overexpression and loss of specificity of the androgen receptor, which then promiscuously binds ligands driving cell survival and proliferation (50).

Adipokines

Leptin and adiponectin are pleiotropic adipocytokines produced and secreted by adipose tissue. As body fat stores increase, circulating leptin concentrations increase, whereas adiponectin levels decrease. The obesity-driven imbalance in adiponectin and leptin are considered key factors linking obesity and cancer. Both mediate energy intake by functioning as neuroendocrine signaling hormones that regulate dietary intake (51, 52), metabolism, insulin sensitivity, and inflammation (53–55). Adiponectin and leptin have direct tumor effects regulating both cell proliferation and apoptosis (56).

Leptin

Six leptin receptors have been identified (ObRa–ObRf); however, only ObRb has a functioning intracellular signaling domain. *In vitro* studies have shown that activation of ObRb by leptin stimulates cell proliferation and survival in colon (57, 58), breast (59), endometrial (60), and androgen-independent prostate cancer cells (61). Leptin signaling is executed through activation of several pathways including JAK/STAT3, PI3K/Akt, and ERK 1/2 (62), and these pathways all serve as potential targets for cancer prevention and control. Leptin also transactivates the EGFR, Notch, and Survivin pathways, and stimulates tumor invasion and migration (63). Leptin can modulate tumor growth by increasing expression of VEGF, a key driver of angiogenesis (64). In animal models, leptin deficiency inhibits mammary tumor growth (65), whereas higher levels are promotional (66). Using azoxymethane to induce colon carcinogenesis in mice, Endo and colleagues showed that leptin signaling through STAT3 resulted in significantly higher tumor proliferation and growth, whereas leptin deficient mice had significantly lower proliferation and smaller tumors despite being more obese (67). In contrast, Ribeiro and colleagues inoculated mice with RM-1 murine androgen-independent prostate cancer cells and found that higher leptin concentrations did not increase prostate cancer tumor growth (68). Thus, disparate effects have been observed across cancer types.

In epidemiologic studies, the link between leptin and cancer has also proven inconsistent. In a nested case–control study in Japanese women, leptin was significantly associated with colorectal cancer after adjusting for several

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risk factors including body mass index (BMI) (69). In contrast, a case–control study in the United States did not find an association between leptin and colorectal adenoma risk in women, but did observe a 3-fold increased risk among men when comparing the highest tertile against the lowest (70). Gender differences in leptin-related risk for colorectal cancer also have been observed (71). Likewise, the data on leptin and risk for breast cancer are conflicting with one study reporting a positive association (72), whereas others reported no association (73, 74), or an inverse association (confined to premenopausal breast cancer; ref. 75). In endometrial cancer, a positive association with leptin was found for 2 studies, although in one, this relationship disappeared after adjusting for BMI (76, 77). For prostate cancer, leptin does not seem to increase overall risk (78–80), however, it may be linked with more aggressive disease (81). In addition, recent studies suggest that absolute levels of leptin may not be the driving force behind neoplasia, but rather it is the ratio of higher leptin in the presence of low adiponectin that confers risk (82).

Adiponectin

There are 2 receptors for adiponectin, AdipoR1 and AdipoR2, which are expressed ubiquitously. Binding of adiponectin to its receptors stimulates phosphorylation of 5′-adenosine monophosphate–activated protein kinase (AMPK), a nutrient-sensing enzyme, which regulates several key pathways involved in cellular energy metabolism and protein synthesis (83). *In vitro*, adiponectin induces apoptosis (84) and inhibits growth and proliferation of breast (85–87), colon (88), endometrial (84), and androgen-dependent and -independent prostate cancer (89). Adiponectin also sequesters several circulating growth factors (90) and inhibits angiogenesis by inducing apoptosis of endothelial cells (91). Studies using preneoplastic murine colon cells have shown that adiponectin inhibits leptin and IL-6–induced cell proliferation by blocking activation of NF-κB and STAT3 (92). Similarly, in late-stage colon cancer cells, adiponectin inhibits IL-6–induced cell proliferation (93). Many, but not all (94) studies using animal models have shown that lower adiponectin results in increased colon tumor growth (95). Interestingly, in the mouse mammary tumor virus (MMTV)-polyoma middle T antigen (PyMT) mammary tumor model, adiponectin-deficient mice have reduced onset and size of mammary tumors as a result of reduced angiogenesis compared with wild-type mice (96, 97).

Data from epidemiologic investigations suggest a role for adiponectin in reducing the risk of several cancers. Consistent with *in vitro* studies, but in contrast to animal models, a consistent association between higher adiponectin concentrations and decreased risk for postmenopausal breast cancer, as well as disease recurrence and mortality has been found repeatedly (98–102). Most studies have also reported that higher adiponectin levels are associated with lowered risk for endometrial cancer (102–105). A recent meta-analysis of 13 studies examined the association between adiponectin and colorectal cancer and adenomas and found a significant reduction in risk for men but not for women (106). For prostate cancer, the data are conflicting and may reflect discrepant associations in aggressive versus indolent disease (107, 78).

Intracellular Pathways

PI3K/Akt/mTORC1

Rapamycin, a caloric restriction mimetic and potential chemopreventive agent, effectively blocks mTORC1 complex formation, thus inhibiting mTORC1-mediated cellular growth and proliferation (108, 109) and has been shown to extend lifespan in mice (110). Furthermore, rapamycin has been shown to suppress tumorigenesis in several animal models (111–115) and inhibits tumor promotion by blocking mTORC1 signaling through p70S6K and cell-cycle proteins PCNA and cyclin D1 (116). Rapamycin also exerts anti-inflammatory effects, and reduces 12-O-tetradecanoylphorbol-l3-acetate (TPA)–induced infiltration of several types of inflammatory cells (117). Collectively, these findings suggest that rapamycin may function as a potent compound in cancer prevention. EGFR activation, likewise, is modulated by caloric intake and may also influence Akt and mTORC1 signaling and EGFR activation via IGF-IR/EGFR cross-talk (118).

5′-Adenosine monophosphate–activated protein kinase

Under conditions of caloric restriction, mTORC1 signaling is inhibited, leading to cell-growth arrest, inhibition of protein translation, and autophagy (118, 119). AMPK and the upstream kinase, LKB1, function to repress mTORC1 in the presence of negative energy balance through activation of TSC1/2. Low ATP/AMP ratios activate AMPK, and phosphorylation is maintained by LKB1 (120). Activation of this pathway not only reduces cellular energy expenditure, but it also protects against stress-induced apoptosis. Studies using *in vivo* models provide evidence that the antidiabetic drug, metformin, which inhibits gluconeogenesis through indirect activation of AMPK, can inhibit tumor formation. Administration of metformin suppresses polyp formation in Apc/Min mice (121). Using paired isogenic colon cancer cell lines (HCT116 $p53^{+/+}$ or $P53^{-/-}$), Buzzai and colleagues (122) were able to show that metformin inhibited the growth of xenograft tumors derived from the p53 null cell line. Also, daily exposure to metformin attenuated tumorigenesis (lymphoma; intestinal polyps) in PTEN-deficient mice (123).

Epidemiologic studies have suggested that diabetic patients receiving metformin have significantly reduced cancer burden compared with diabetic patients receiving other therapies (124). Recent studies have also suggested that metformin may be more effective in overweight/obese individuals or in individuals with elevated insulin levels (12), and clinical trials are now underway to evaluate the effect of metformin for the prevention of recurrence of breast cancer.

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Immune Cells and Inflammatory Factors

Macrophage infiltration

Chronic inflammation has long been associated with cancer development and progression and increases the risk of multiple tumor types (9). Obesity leads to subclinical inflammation in visceral and subcutaneous white adipose tissue (WAT), characterized by macrophages surrounding necrotic adipocytes and forming crown-like structures (CLS) (125–127). Increased numbers of CLS were shown within the mammary glands of obese mice, accompanied by activation of NF-κB, increased levels of proinflammatory mediators, and higher levels and activity of aromatase and its activity, thus driving the synthesis of estrogen (and perhaps ER+ breast cancer) (42). These findings support the possibility that the obesity → inflammation axis is important for breast carcinogenesis.

In women, CLS of the breast (CLS-B) were found in nearly 50% of patient samples (43). The severity of breast inflammation, defined as the CLS-B index, correlated with BMI and adipocyte size, and may serve as a biomarker of increased breast cancer risk or poor prognosis. Consistent with the preclinical findings, increased NF-κB binding activity, increased levels of proinflammatory mediators, and elevated aromatase expression and activity were found in the inflamed breast tissue of overweight and obese women (43, 44). The discovery of the connection between obesity, breast inflammation, and changes in the expression of genes linked to breast cancer suggests the possibility that interventions, which reduce breast inflammation may decrease the increased risk of breast cancer in obese postmenopausal women.

Cytokines

Increasing adiposity has been shown to be positively associated with inflammation in both rodents and humans (128). The increased adipose tissue associated with obesity, especially WAT, produces many inflammatory cytokines, including TNF-α, IL-6, IL-1β, monocyte chemoattractant protein (MCP-1), and C-reactive protein (CRP), which act both locally (tissue level) and globally (circulating in serum) (129). Increased adipose-derived cytokine production, particularly increased levels of MCP-1, enhances local macrophage infiltration, leading to further increases in the levels of secreted inflammatory cytokines as well as heightened recruitment of other related immune cells (129–131). These inflammatory cytokines modulate inflammation via increased intracellular signaling through NF-κB-, STAT3-, and c-*jun*-NH2 terminal protein-kinase (JNK)–related pathways (129, 132), which are inhibited by caloric restriction (133). These findings suggest the possibility that diet-induced changes in inflammation may modulate tumor development and progression.

NF-κB

At the intracellular level, inflammation is mediated through multiple pathways. NF-κB is a transcription factor activated in response to various stimuli including growth factors and inflammatory molecules, and is responsible for inducing gene expression associated with cell proliferation, apoptosis, angiogenesis, and inflammation (134). Activation of NF-κB has been observed in many tumor types and has emerged as an important target for cancer drug development (135). Obesity and caloric restriction modulate NF-κB activation, possibly through alterations in growth factors and Akt signaling (134, 136). Activation of NF-κB by Akt can lead to the translocation of the active NF-κB subunit, p65, from the cytoplasm to the nucleus, inducing multiple genes associated with inflammation and cancer, including IL-6, COX-2, and IL-1β (134). Thus, NF-κB represents an attractive drug target for attempting to reduce the risk or progression of cancer.

Systems Level Considerations

Diet composition

While there is a clear association between obesity and cancer in both humans and animal models, it is frequently difficult to distinguish the consequences of diet composition from those of obesity. Studies in humans, largely based on observational research, especially those on international differences in dietary fat consumption and cancer incidence, as well as, on a limited number of case–control studies, are suggestive of an association between dietary fat and increased risk of breast, colorectal, and prostate cancers. However, results of these studies are mixed and confounded by body weight status (137–139). In addition, 2 large randomized control trials, The Women's Healthy Eating and Living (WHEL) study (140) and The Women's Intervention Nutrition Study (WINS; ref. 141) evaluated the effect of dietary modification on cancer recurrence and survival in women with early-stage breast cancer. The WINS study reported borderline significance for an association between dietary fat and "breast cancer events," whereas the WHEL study found no significant association between fat and breast cancer recurrence (140–142). Comparison of these studies is confounded by multiple differences, among which is the ability to separate the reduction in dietary fat from weight loss (140–142).

To investigate the individual contribution and to bypass the confounding issues associated with genetics, dietary fat, and obesity, experiments were carried out capitalizing on the observation that C57BL/6 mice fed a high-fat diet become obese, whereas A/J mice fed the same diet remain lean. Taking advantage of these genetic differences, a series of crosses were conducted between the B6 and A/J mice to generate chromosome substitution strains (CSS) of mice in which each pair of homozygous A/J chromosomes were substituted on an otherwise B6 genetic background (143). These CSSs provide a series of B6 strains that are susceptible or resistant to diet-induced obesity based on a single pair of A/J chromosomes. Further research has focused on separating the effect of dietary fat from obesity, using CSSs in combination with B6. $Apc^{Min/+}$ mouse models of intestinal cancer were used to generate congenic-consomic strains (C-CS). Using C-CSs that were susceptible to $Apc^{Min/+}$ intestinal tumors and were either susceptible or resistant to diet-induced obesity depending on the substituted A/J

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chromosome, it was shown that a high-fat diet versus low-fat diet (58% vs. 10%) resulted in significant increases in intestinal polyp numbers, tumor burden, and shorter survival time independent of obesity. Moreover, mice fed the high-fat diets showed increases in inflammatory cytokines in the sera (IL-6 and IL-1β) and in intestinal tissue (TNF-α, Cox-2, IL-1β, and IL-6). These studies clearly show that a high-fat diet, independent of obesity, can upregulate intestinal and circulating inflammatory mediators, and increase intestinal polyp growth and tumor burden leading to shorter survival (144). These studies support the use of low-fat diets as a cancer prevention strategy, at least for some cancer types, and suggest that anti-inflammatory agents may also be useful in preventing high-fat diet–induced carcinogenesis. In view of the WINS and WHEL trials, these studies with mouse CSSs point to the need for randomized controlled trials of dietary fat modification for primary prevention, especially as the WHI study showed that the low-fat diet resulted in a reduction in primary breast cancer of borderline significance (145), and significantly reduced ovarian cancer (146). Moreover, diet studies during critical windows of susceptibility along the lifecourse are needed. In particular, studies occurring during the critical periods associated with breast bud development in the early years of life also are needed.

Exercise

As recently reviewed, exercise interventions have been associated with reduced risk of some types of cancer in humans, with convincing evidence that the exercise–cancer link is independent of body weight status for colon, breast, and endometrial cancers; weak evidence for prostate, lung, and ovarian; and either null or insufficient data for other cancer types (147). Studies examining the effects of exercise on carcinogenesis have used a variety of animal models and many, but not all, studies report some evidence of a protective effect of either voluntary or involuntary exercise on carcinogenesis. The strength and direction of the association depend on cancer type, intensity of the exercise regimen, and whether food intake was held constant or provided *ad libitum*. Zhu and colleagues recently reported that plasma markers with the greatest predictive value of the anticancer effects of both moderate caloric restriction and moderate exercise in a carcinogen-induced rat mammary model were adiponectin, bioavailable IGF-I, and leptin (148). In other models, exhaustive exercise has been linked to increased reactive oxidative stress and inflammation, and increased tumor development (149), whereas moderate exercise can often be anti-inflammatory (150). Given the inherent links between exercise and energy balance, the effects of exercise *per se*, independent of decreased energy balance remain unclear. A study of gene expression profiles in normal mammary tissues of 9-week-old C57BL/6 mice that were randomized to caloric restriction and/or exercise, however, suggests that pathways may differ considerably as caloric restriction modified gene expression in 425 genes, whereas physical activity modified expression in just 45, with overlap noted in only 3 genes (151). Results of recent clinical trials in healthy volunteers suggest that weight loss may exert a more powerful effect on biomarkers associated with inflammation and sex steroid pathways (152, 153). Recent studies in mice show that exercise reduces systemic insulin resistance by an autophagy-inducing process. The latter could provide a mechanism for exercise to reduce tumor growth through a process of reduced levels of circulating insulin (154).

Cancer stem cells

Cancer stem cells, their role in carcinogenesis and progression, and their potential as targets for cancer prevention and therapy, has become a major focus of cancer research. Moreover, as described later, cancer stem cells may provide targets for some of the proliferation-stimulating effects of adipocytokines elevated in obesity. Tissue stem cells are a population of cells with the capacity to undergo self-renewal and multilineage differentiation into the normal cell population that constitute tissues and organs. The cancer stem cell hypothesis postulates that tumors originate through dysregulation of the normal self-renewal process resulting in the aberrant replication and differentiation characteristic of a variety of tumors. Clonal expansion of these aberrant cells has recently been confirmed by lineage tracing in mouse intestinal adenomas (155) and is an early step in carcinogenesis. In addition to being responsible for primary tumorigenesis, the cancer stem cells may be resistant to chemotherapeutic agents and responsible for tumor recurrence and metastasis. Thus, strategies aimed at limiting proliferation of these stem cells may be useful for both primary and secondary cancer prevention.

A new linkage between obesity and tumor stem cells has recently been identified by Zheng and colleagues (65) who showed that spontaneous tumors derived from murine mammary tumor virus–Wnt-1 transgenic mice, when transplanted, were highly leptin-dependent for growth. Thus, transplantation of these tumors into obese, leptin receptor–deficient mice (db/db) with high leptin concentrations, grew to 8 times the volume of those tumors transplanted into wild-type mice, whereas in leptin-deficient (ob/ob mice), tumor growth and overall tumor burden was reduced. The residual tumors in ob/ob mice were found to have fewer "stem cells" and these cells were characterized by flow cytometry to express LepRb (65). When isolated by LepRb expression, these cells exhibited stem cell properties of tumorsphere formation *in vitro*, and their survival was regulated by leptin. Dunlap, and colleagues report that M-Wnt mammary tumor cells derived from Wnt-1 tumor profile with human claudin-low breast tumors, are mesenchymal and stably enriched in breast cancer cell markers, and exhibit stem cell properties (156). In addition, M-Wnt cells orthotopically injected into B6 mice rapidly form claudin-low tumors that are highly responsive to the tumor-enhancing effects of obesity, as well as the anticancer effects of calorie restriction (156). Relationships between obesity, adipose tissue cytokines, and stem cell biology also can be readily studied *in vitro* directly from human breast tissue excised during elective reduction mammoplasty

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(157). However, at present, human clinical trials specifically targeting stem cells are hampered by the need for large volumes of breast tissue (e.g., from mammoplasty or mastectomy) for stem cell isolation and dynamic assays, such as *in vitro* tumor sphere formation as biomarker endpoints (158). Therefore, current efforts are focused upon using core biopsy samples for stem cell isolation and characterization using advanced *in situ* technologies, such as multiplex imaging or profiling technologies.

Conclusions and Future Directions

While much current research focuses on selected signaling pathways, this review emphasizes the numerous mediators and pathways by which obesity impacts cancer. Many of the circulating signaling molecules bind to cell surface receptors where they activate intracellular pathways, which undergo cross-talk and activate intracellular downstream pathways that both converge and diverge to promote cancer cell growth and metastasis.

These observations suggest several strategies for prevention and therapy for obesity-mediated cancer promotion including, (i) prevention and treatment of obesity; (ii) blocking synthesis and release of the signaling molecules including hormones, cytokines, and adipokines; (iii) blocking binding and activation of direct targets including cell surface and hormone receptors; (iv) blocking downstream intracellular pathways, such as the P13K, Akt, and mTOR pathway; and (v) disrupting inflammatory pathways at both the cellular and systemic levels. This list might suggest that it should be easy to prevent cancer by blocking one or several of these pathways. However, Table 1 provides a partial list of 14 of the manifold obstacles to prevention of obesity-associated cancers. These obstacles are divided into 2 major categories, the first being obstacles to disrupting obesity promotion of cancer, and the second being obstacles to obesity control. Most of the factors listed in the first group have been discussed earlier in terms of defining their role in mediating the effect of obesity on cancer. The plethora of pathways connecting obesity to cancer suggests that while targeting any one of these pathways may provide potential interference with cancer cell growth, the cancer cell has established alternative and redundant processes and pathways to evade control and bypass road blocks at any one site. Thus, an important area for future research is to determine how to control obesity, as well as its downstream effects. Innovative approaches to these issues are imperative as are mechanistic studies and clinical trials on the effects of caloric restriction, exercise, and potential pharmacomimetics of these processes.

With regard to the second group, obesity control is obviously critically important to multiple disorders, but a careful review of issues related to obesity prevention or reversal is beyond the scope of this article. Nonetheless, several of the major obstacles involved in its prevention and control are listed, as they must be dealt with by any approach to disrupt the linkage between obesity and cancer.

Just as prevention and control of diabetes, hypertension, and cardiovascular disease require multifactor and multilevel approaches, including diet, physical activity, and behavioral modification, as well as pharmacologic and surgical interventions for subsets of individuals, so too it is likely that multipronged, transdisciplinary approaches will be required to disrupt the obesity–cancer linkage. The recent estimate that the incidence of obesity in the United States will reach 42% by 2030 emphasizes the urgent need for this research (159).

Table 1. Obstacles to prevention of obesity-associated cancers

Obstacles to disrupting obesity promotion of cancer

1. Multiplicity of obesity-driven extracellular hormone and growth factors promoting tumor cell growth, for example, insulin, IGF-1, leptin, estradiol, etc.
2. Multiplicity of obesity-driven extracellular inflammatory factors, for example, IL-1β, IL-6, TNF-α, etc.
3. Receptor hybridization, cross-talk and multiplicity, for example, IR, IGF receptor, leptin receptor, etc.
4. Multiplicity and cross-talk among intracellular pathways activated by obesity mediators, for example, PI3K–Akt–mTOR, JAK2–STAT3–MAPK, NANOG–SOX, and EGFR–Notch1–Survivin.
5. Multiplicity of cellular targets, for example, cancer cells, cancer stem cells, tumor microenvironment, vascular endothelium, etc.

Obstacles to obesity control

6. Genetic programming for energy storage
7. Abundance of high-energy density foods
8. Poor adherence to caloric restriction
9. Inadequate sleep
10. Sedentary lifestyles and proliferation of energy saving devices
11. Built environment impediments to physical activity
12. Cost and accessibility of exercise equipment and programs
13. Absence of effective pharmacologic interventions
14. High cost and consequences of bariatric surgery

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